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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 March 2003 (20.03.2003)

PCT

(10) International Publication Number
WO 03/023432 A1

(51) International Patent Classification[7]: G01R 33/28, A61K 49/18

(21) International Application Number: PCT/NO02/00321

(22) International Filing Date:
12 September 2002 (12.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0122049.0 12 September 2001 (12.09.2001) GB

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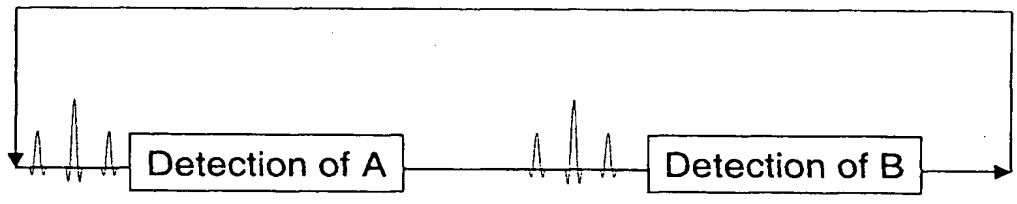
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A METHOD OF USING SPECTRAL-SPATIAL EXITATION AT MAGNETIC RESONANCE IMAGING



(57) Abstract: The present invention provides a method of magnetic resonance imaging of a sample, said method comprising: administering a hyperpolarised MR imaging agent comprising non-zero nuclear spin nuclei into said sample; exposing said sample to a radiation at a frequency selected to excite nuclear spin transitions in said non-zero nuclear spin nuclei; detecting MR signals from said sample utilising spectral-spatial excitation, in combination with line scanning, point scanning and/or steady state imaging techniques; and optionally generating an image, physiological data or metabolic data from said detected signals.

WO 03/023432 A1

A METHOD OF USING SPECTRAL-SPATIAL EXITATION AT MAGNETIC RESONANCE IMAGING

The present invention relates to methods of magnetic resonance imaging (MRI), in particular to the study of metabolites and methods of extracting metabolic information.

In order to achieve effective contrast between MR images of different tissue types, it has long been known to administer to a subject under examination MR contrast agents (the term "MR contrast agent" in the context of the present application can be interchangeably used with the term "imaging agent", "MR imaging agent" or "contrast agent"), e.g. paramagnetic metal species which affect relaxation times in the zones in which they are administered or at which they congregate. MR signal strength is dependent on the population difference between the nuclear spin states of the imaging nuclei . This population difference is governed by a Boltzmann distribution and is dependent on temperature and magnetic field strength.

Techniques have been developed which involve *ex vivo* nuclear spin polarisation of agents containing non zero nuclear spin nuclei (e.g. ^{3}He, ^{13}C, ^{15}N,), prior to administration and MR signal measurement. The term "polarisation" in the context with the present application can be interchangeably used with the term "hyperpolarisation". Some such techniques involve the use of polarising agents, for example conventional OMRI imaging agents or hyperpolarised gases to achieve *ex vivo* nuclear spin polarisation of non zero nuclear spin nuclei in an administrable MR imaging agent. By polarising agent is meant any agent suitable for performing *ex vivo* polarisation of an MR imaging agent.

In MRI methods involving *ex vivo* nuclear spin polarisation, the signal is obtained directly from the nuclei of the agent, as opposed to conventional MRI, where the signal is obtained from protons, which in turn are affected by the paramagnetic contrast agent. The hyperpolarized MR imaging agents should comprise in their molecular structure nuclei capable of emitting MR signals in a uniform magnetic field (e.g. MR imaging nuclei such as ^{13}C or ^{15}N nuclei) and capable of exhibiting a long T_1 relaxation time, and preferably additionally a long T_2 relaxation time. Such agents are referred to hereinafter as "high T_1 agents". A high T_1 agent, a term which does not include ^1H_2O, will generally be water-soluble and have a T_1 value of at least 6 seconds in D_2O at 37 C and at a field of 7 T, preferably 8 secs or more, more preferably 10 secs or more, especially preferably 15 secs or more, more especially preferably 30 secs or more, yet more especially preferably 70 secs or more, even yet more especially preferably 100 secs or more. Unless the MR imaging nucleus is the naturally most abundant isotope, the molecules of a high T_1 agent will preferably contain the MR imaging nucleus in an amount greater than its natural isotopic abundance (i.e. the imaging agent will be "enriched" with said nuclei).

Several ways of hyperpolarising compounds comprising long T_1 nuclei, e.g. ^{13}C or ^{15}N nuclei, to produce imaging agents are known. For example, it is possible to use the 'para-hydrogen method' - see Applicant's own earlier International Publication No. WO-A-99/24080 - or dynamic nuclear polarisation (DNP) - see WO-A-99/35508, both of which are herein incorporated in their entirety.

The use of hyperpolarised MR imaging agents in MR investigations such as MR imaging has the advantage

over conventional MR techniques in that the nuclear polarisation to which the MR signal strength is proportional is essentially independent of the magnetic field strength in the MR apparatus. Currently the highest obtainable field strengths in MR imaging apparatus are about 17 T, while clinical MR imaging apparatus are available with field strengths of about 0.2 to 3.0 T. Since superconducting magnets and complex magnet construction are required for large cavity high field strength magnets, these are expensive. Using a hyperpolarised imaging agent, since the field strength is less critical it is possible to make images at all field strengths from earth field (40-50 μT) up to the highest achievable fields.

Conventionally, detection of the MRI signal in MRI methods following the administration of a hyperpolarised contrast agent into a sample is via one of the standard Fourier-based methods (e.g. spin warp, EPI etc.). If the contrast agent for example comprises a compound of interest in metabolic studies, it is in this way possible to visualise the concentration of a given metabolite. In such methods, the required resolution of the image will determine the number of phase-encoding steps required. When a fast gradient echo sequence is applied, such as FLASH, the total scan time equals the number of phase-encoding steps multiplied by the repetition time. Thus, to obtain high resolution, many phase-encoding steps are required and hence the scan time will be relatively long.

When a hyperpolarised imaging agent is employed and in order to detect and visualise the changes in metabolite concentrate at two or more locations, the pulse sequence, at least when a standard Fourier transform (FT) method is used, must also collect data from areas outside of the specific "regions of

interest" (ROI). The nature of the standard FT method means that it is in fact necessary to collect data from a complete 'slice'. After the scan, the data obtained can be reconstructed into an image.

The desired spatial resolution in the ROI's will in itself dictate the number of phase-encoding steps required to sample the complete slice plane. Hence, if a high spatial resolution is required in a given ROI, a large number of phase-encoding steps will be required. This translates to a large number of excitation pulses and - as the magnetisation is divided between all the excitation pulses when using a hyperpolarised contrast agent - to a lower signal-to-noise ratio (SNR).

In the technique of chemical shift imaging, the pulse sequences used are multi-dimensional, that is at least one spatial dimension and one frequency dimension. Thus, when sampling along a slice, a strong gradient is used followed by two spatial (phase) encoding gradients. Signal collection is then performed without any gradient. In methods utilising hyperpolarised MR agents, magnetisation is divided between all the excitation pulses, thus leading to a low SNR.

In its broadest sense, the present invention relates to a method which is utilising the spectral-spatial excitation technique and which is performed after the administration of an imaging agent to a sample.

Thus viewed from one aspect the present invention provides a method of magnetic resonance imaging of a sample, preferably a human or non-human animal body (e.g. a mammalian, reptilian or avian body), said method comprising:

i) administering a hyperpolarised MR imaging agent comprising non-zero nuclear spin nuclei into said sample;

ii) exposing said sample to a radiation at a frequency selected to excite nuclear spin transitions in said non-zero nuclear spin nuclei;

iii) detecting MR signals from said sample utilising spectral-spatial excitation, in combination with line scanning, point scanning, single voxel detection and/or steady state imaging techniques, preferably in combination with steady state imaging techniques; and

iv) optionally generating an image, physiological data (e.g. pH, pO_2, pCO_2, temperature or ionic concentrations) or metabolic data from said detected signals.

If the method according to the invention is used to generate metabolic data, MR signals according to step iii) are detected after the imaging agent has left the vascular bed.

One way to alleviate the problem of low SNR as noted above is that instead of collecting a three-dimensional data set (over at least one spatial and one frequency dimension), images containing information only from specific peaks at known positions in the MR spectrum are generated. In this manner, the number of required excitations is reduced and hence the SNR is raised.

As such, the method as described above may be used to extract metabolic information. For instance, if the imaging agent comprises a hyperpolarised compound which is of interest in metabolic studies and the T_2

value of the metabolite in question is long, then the complete data collection may be performed after only one excitation of the metabolite. Hence, the SNR will be increased.

In order to collect image information from two or more metabolites, the MR spectrum must be known. The separation during the image pulse sequence is then performed using a combination of spectral and spatial selective rf excitations and standard gradient pulses. By performing the excitation using composite binomial pulses it is possible to bring one component, A say, of a two metabolite-component system, A and B say, into the xy-plane, whilst leaving the B component in the z-direction. Thus, the component of metabolite A can be separately detected. After this detection, component B can be similarly rotated into the xy-plane and detected separately.

The effective T_2 relaxation time will determine whether the detection stage outlined above includes only one phase-encoding step or all the phase steps needed to reconstruct a complete image. Subsequent to the first detection interval, the peak corresponding to the second metabolite is excited using the same type of composite pulse and then the generated xy-magnetisation is detected. This sequence is shown schematically in Figure 1 of the accompanying drawings.

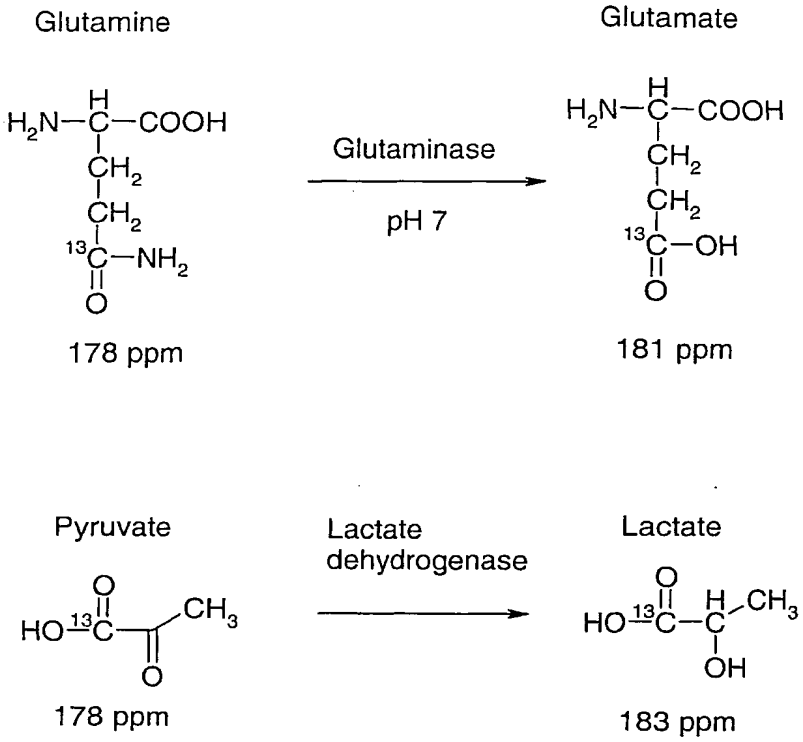
If the T_2 relaxation time of the metabolites is short, then the sequence shown in Figure 1 is repeated in order to collect all the phase-encoding steps needed to reconstruct images showing the spatial distribution of the two metabolites.

However, if the T_2 values of the metabolites are long, for example of the order of a few 100 milliseconds or

more, preferably 200 milliseconds or more, more preferably 500 milliseconds or more, most preferably 1000 milliseconds or more, so-called single shot detection schemes can be employed, for example spiral or EPI gradient readout sequences. If, on the other hand, the T_2 values of the metabolites are short, for example of the order of 50 milliseconds or shorter, preferably 35 milliseconds or shorter, more preferably 20 milliseconds or shorter, most preferably 10 milliseconds or shorter, single shot detection cannot be used. Short T_2 values on this scale means that 'new' z-magnetisation corresponding to a specific metabolite is constantly created and thus the detection stage is carried out using several excitations.

The method of this aspect of the present invention thus makes it possible to either simultaneously or in an interleaved fashion, detect the contribution from two or more metabolites present in the same slice plane.

Preferably, the hyperpolarised MR imaging agent should comprise a compound of interest in metabolic studies. For example, the compounds shown in the schemes below are particularly suitable. In each case, the chemical shift values of the respective ^{13}C nuclei are given.



The present invention also relates in a further aspect to a method whereby MR signals are detected by line scanning (LS) whereby the above-mentioned drawbacks of lower SNR's can once again be alleviated. In this aspect, the detection step (iii) above comprises line scanning, preferably in combination with steady state imaging techniques.

When using the line scanning (LS) aspect of the invention, data from discrete lines are collected, wherein said lines include the ROI's. This has the advantages of reducing the required scan time compared to conventional FT techniques and also reduces the susceptibility of the method to both movement of the subject being imaged and blood flow. Indeed, it is found that the SNR expected from the present LS method when hyperpolarised contrast agents are used, is the

same as the one delivered by a variable flip angle gradient echo (VFA-GE) sequence. In other words, the loss of SNR usually found when hyperpolarised contrast agents are used in methods incorporating conventional FT techniques is eliminated or at least reduced.

A suitable LS pulse method is shown in Figure 2 of the accompanying drawings. It is shown in Figure 2 that the combination of one 90 and one 180 pulse together with gradient pulses excites two tilted planes through the imaged object and thus only the MR signal from the cross-section, that is, a discrete line, will be detected.

Consequently, in this method, it is only the MR signal from the discrete line that is sampled during the sample window. Z-magnetisation outside the selected line is essentially untouched and may be detected by successive pulses. Hence, only information needed to reconstruct lines which include the ROI are collected. The number of lines required will depend on the selected resolution.

Thus, if information is only required from restricted areas, i.e. when information is required on metabolites following the administration of a contrast agent comprising a hyperpolarized compound which is of interest in a metabolic study, it is possible to significantly reduce the scan time by using the LS method herein described, rather than the standard VFA-GE method. Furthermore, this method has the advantage that it is less sensitive to movements, i.e. phase artefacts, and the method may be extended to a multi-echo version which makes it possible to obtain images with different T_2 weightings.

A further aspect of the present invention is to use so-called point scanning or single voxel detection.

In this aspect, the detection step (iii) above comprises point scanning or single voxel detection, preferably in combination with steady state imaging techniques.

In this latest aspect, the spins of the nuclei in a volume element (voxel), i.e. in a ROI, are excited using a 90 pulse and then the MR signal is collected. As the volume elements under investigation can be limited to the specific ROI, the total scan time is significantly reduced. Using this method it is possible to obtain comparable SNR values for studies with hyperpolarised contrast agents as could be obtained using a standard VFA-GE sequence.

A suitable pulse sequence capable of collecting the signal from a single voxel in the manner of this aspect of the present invention is shown in Figure 3 of the accompanying drawings. It is shown in Figure 3 that the combination of three rf pulses together with a 90 gradient pulse excites three tilted planes through the imaged object and only the MR signal from the discrete voxel will be detected.

When the standard gradient echo (GE) or spin echo (SE) sequences are used, a high SNR is achieved using several excitations after which the MRI-signal from the complete imaged slice or volume is collected. Between the excitations the z-magnetization is partly completely restored. However, when hyperpolarized media are used this is found not to be the case. No new z-magnetization is created. Instead the z-magnetization is split due to the applied rf pulses. Previously, the variable flip angle (VFA) approach has been used. In this technique the flip angle of the excitation pulses are calculated using the expression $\alpha_{n-1} = \arctan(\sin(\alpha_n))$, where α is the flip angle (FA). If the effect due to T_1-relaxation during the

sequence is ignored, all xy-magnetization components, generated after each excitation pulse, will have the same amplitude. In the case of a hyperpolarised gas (e.g. ^{129}Xe, ^{3}He) the T_1 value is of the order of several seconds and thus the assumption is valid. A hyperpolarised ^{13}C-contrast agent will also have very long T_1 and T_2 values. However when metabolites of said contrast agent are visualized, one has to take into account the mean life-time of the metabolite in question.

When chemical shift imaging (CSI) is performed in order to obtain ^{1}H-spectra the number of excitations has to at least equal the number of matrix elements. Figure 4 of the accompanying drawings illustrates how a 16 x 16 matrix may be placed in order to collect the ^{1}H-spectrum from the ROI's. While both the x- and the y-directions are phase encoded, this method of collecting the MRI-signal will have the same effect as using an average factor of N_xN_y, where N_x and N_y are the number of matrix elements in the x- and y-directions, respectively. Consequently, this will result in an increased SNR with a factor of 16 (equal to the square root of N_xN_y for a 16x16 matrix) compared to the situation if one where to collect the signal from each volume element separately using a single point scanning method. This factor is valid only if long TR is used, thus allowing the proton z-magnetization to be fully restored after each excitation. The pixel size will determine the size of the matrix size required. If this scheme were to be used in combination with hyperpolarised contrast agent, the available z-magnetization would need to be split into 256 (= 16 x 16) excitations and thus the scan time would equal (256 x TR). This splitting may be performed using VFA.

With the method according to the invention using point scanning, data can be collected from the dark ROI's indicated in Figure 5 of the accompanying drawings only, thus, the total scan time would be reduced to (24 x TR).

In addition, it is necessary to consider the effect on the SNR. A simulation system, based on a k-space partition model, has been used to evaluate the SNR in a VFA-CSI sequence compared to a single point scanning method.

The phantom objects, used to compare the expected relative SNR of the point scan (PS) method with a standard variable flip angle chemical shift image (VFA-CSI) sequence, are shown in Figure 6 of the accompanying drawings. The volume of a given point (A in Figure 6) extracted from the imaged sample using the PS method corresponds to the volume represented by one single element in the image matrix (B in Figure 6) generated using the VFA-GE sequence. The results of the simulations demonstrate, that the LS- and PS methods give a comparable SNR to the VFA-CSI method, as long as an hyperpolarised imaging agent is used.

Thus, if information is only required from restricted areas, i.e. when information is required on metabolites following the injection of hyperpolarised contrast agents, it is possible to significantly reduce the scan time by using the PS method herein described compared to the scan time using the VFA-CSI approach. Furthermore, this aspect has the advantage that by reducing the scan time it becomes possible to measure local changes in the concentration of metabolites since the temporal resolution is increased. This aspect may also advantageously be used to measure the inflow of hyperpolarised contrast

agents to a restricted volume, e.g. to a voxel, due to flow, diffusion or perfusion.

The final aspect of the present invention relates to methods involving steady state imaging techniques e.g. by using pulse sequences specially adapted to successfully image hyperpolarised agents with long relaxation times.

Previously, most experiments with hyperpolarised agents have focused on lung ventilation using hyperpolarised noble gases. In such experiments, rapid pulse sequences with small flip angles, e.g. FLASH are used, due to the short T_2 times of the gases in the lungs. By using hyperpolarised agents containing nuclei with extremely long relaxation times, e.g. ^{13}C nuclei typically with T_1 and T_2 values greater than 10 secs, new possibilities arise in the field of physiological mapping.

When the repetition time (TR) between successive RF-excitations is short compared to the T_2 relaxation time, transverse magnetization will survive long enough to contribute to the signal collected during several successive TR intervals. This effect is referred to as "steady state" and has been thoroughly analyzed in Magn. Res. Imaging, Vol. 6 (1988), 355-368. When the signal comes from a hyperpolarised agent, a true steady state cannot be established. However, if the total duration of the imaging sequence is short compared to the T_1 relaxation time and T_2 is long compared to TR, a "pseudo steady state" (in the following, the term "steady state" is used for "pseudo steady state" also) is established. This cannot occur when imaging the lung ventilation using hyperpolarised gases (since T_2 and T_2^* values are too low), but can easily be the case when utilizing a hyperpolarised agent (e.g. comprising ^{13}C or ^{15}N) in liquid phase.

When a steady state situation is reached the signal amplitude from a region where the hyperpolarised imaging agent is present will be constant and the attenuation of it will be a mix of T_1 and T_2 relaxation. If the pulse sequence used is a fully balanced gradient echo sequence (e.g. true FISP) the T_2 part of the attenuation will be a function of T_2 and not T_2^*, as is common in gradient sequences. Thus, the fully balanced version of gradient sequences is the preferred choice.

The FISP and PSIF pulse sequences described in Magn. Res. Imaging, Vol. 6 (1988), 355-368 are two possible sequences for steady state imaging. However, both FISP and PSIF sequences offer poor T_2 contrast when used with small flip angles. In contrast, higher flip angles (45 - 90) produce a pronounced T_2 contrast, and such sequences have not been described in the literature.

The applications for the method according to the invention using T_2-contrast sensitive sequences include physiological imaging using hyperpolarised imaging agents with long relaxation times. The intrinsic T_2 relaxation rate of the agent may increase (shorter T_2) due to physiological changes (e.g. pH, temperature). If the hyperpolarised imaging agent is metabolized, the apparent T_2 relaxation rate will also increase due to the shorter half-life of the agent, thus giving reduced signal in areas with faster metabolism.

Suitable MR imaging agents for use in the methods of the present invention have been previously described by the present Applicant, for instance in WO-A-99/35508 all of which publications are herein incorporated by reference.

By "hyperpolarised" we mean polarised to a level over that found at room temperature and 1 T, preferably polarised to a polarisation degree in excess of 0.1%, more preferably in excess of 1%, even more preferably in excess of 10%.

The hyperpolarised imaging agent should preferably also exhibit a long T_2 relaxation time, preferably greater than 0.5 secs, more preferably greater than 1 sec, even more preferably greater than 5 secs.

Suitable MR imaging agents for use in the aspects of the invention may contain nuclei such as ^{1}H, ^{19}F, ^{3}Li, ^{13}C, ^{15}N, ^{29}Si, ^{129}Xe, ^{3}He or ^{31}P, preferably ^{13}C and ^{15}N. Most especially preferred are ^{13}C nuclei.

As noted above, ^{13}C and ^{15}N are the nuclei most suited to use in the methods of the present invention with ^{13}C especially preferred. ^{1}H nuclei have the advantages of being present in high concentration in natural abundance and having the highest sensitivity of all nuclei. ^{13}C nuclei are advantageous as the background signal from hyperpolarised ^{13}C nuclei is very low and much less than from, for example, ^{1}H nuclei. ^{19}F nuclei have the advantage of high sensitivity. Hyperpolarisation of imaging agents comprising ^{31}P nuclei allows endogenous substances to be used in all aspects of the present invention.

Where the MR imaging nucleus is other than a proton (e.g. ^{13}C or ^{15}N), there will be essentially no interference from background signals (the natural abundance of ^{13}C and ^{15}N, for instance, being negligible) and image contrast will be advantageously high. This is especially true where the MR imaging agent itself is enriched above natural abundance in the MR imaging nucleus.

The MR imaging agent should preferably be artificially enriched with nuclei (e.g. ^{15}N and/or ^{13}C nuclei) having a long T_1 relaxation time, for example more than 2 s, preferably more than 5 s, especially preferably more than 30 s.

The long T_1 relaxation time of certain ^{13}C and ^{15}N nuclei is particularly advantageous and certain MR imaging agents containing ^{13}C or ^{15}N are therefore preferred for use in the present methods. Preferably the polarised MR imaging agent has an effective nuclei ^{13}C-polarisation of more than 0.1%, more preferably more than 1.0%, even more preferably more than 10%, particularly preferably more than 25%, especially more than 50% and finally most preferably more than 95%.

The MR imaging agent is more preferably ^{13}C enriched at carbonyl or quaternary carbon positions, given that a ^{13}C nucleus in a carbonyl group or in certain quaternary carbons may have a T_1 relaxation time typically of more than 2s, preferably more than 5s, especially preferably more than 30s. Preferably the ^{13}C enriched compound should be deuterium labeled, especially adjacent the ^{13}C nucleus. Preferred ^{13}C enriched compounds are those in which the ^{13}C nuclei are surrounded by one or more non-MR active nuclei such as O, S, C or a double or triple bond.

The MR imaging agent should of course be physiologically tolerable or be capable of being provided in a physiologically tolerable, administrable form with conventional pharmaceutical or veterinary carriers or excipients. Preferred MR imaging agents are soluble in aqueous media (e.g. water).

The formulation, which preferably will be substantially isotonic, may conveniently be

administered at a concentration sufficient to yield a 1 μM to 10 M concentration of the MR imaging agent in the imaging zone. However the precise concentration and dosage will of course depend upon a range of factors such as toxicity and the administration route.

Parenterally administrable forms should of course be sterile and free from physiologically unacceptable agents, and should have low osmolality to minimize irritation or other adverse effects upon administration and thus the formulation should preferably be isotonic or slightly hypertonic.

The dosages of the MR imaging agent used according to the method of the present invention will vary according to the precise nature of the MR imaging agents used and of the measuring apparatus. Preferably the dosage should be kept as low as possible while still achieving a detectable contrast effect. In general, the maximum dosage will depend on toxicity constraints.

After the polarisation, the hyperpolarised MR imaging agent may be stored at low temperature e.g. in frozen form. Generally speaking, at low temperature the polarisation is retained longer and thus polarised imaging agents may conveniently be stored e.g. in liquid nitrogen. Prior to administration, the MR imaging agent may be rapidly warmed to physiological temperatures using conventional techniques such as infrared or microwave radiation.

Embodiments of the invention are described further with reference to the following non-limiting Examples and the accompanying drawings, in which:-

Figure 1 is an example of a pulse sequence used in the first aspect of the present invention (according to claim 1);

Figure 2 is an outline of LS pulse sequence;

Figure 3 is an outline of a PS pulse sequence;

Figures 4 and 5 illustrate how a 16 x 16 matrix (black grid) may be placed to collect the ^{1}H-spectrum from ROI's (white ellipses);

Figure 6 shows phantom objects in the PS method;

Figure 7 shows the results from simulations using both LS and GE sequences;

Figure 8 shows the results from simulations using both PS and CSI sequences; and

Figure 9 shows the results of simulations of experiments with hyperpolarised agents.

EXAMPLE 1 - Line Scanning Method

Figure 7 of the accompanying drawings shows the results from simulations using both LS and GE sequences.

In Figure 7a, an image generated by the LS method is shown and has a SNR of 19.4. The image in Figure 7b is from a GE sequence with a long TR, the latter to ensure full relaxation between excitation pulses, and a flip angle of 90. In this case, the SNR is 226.5. However, the sequence leading to the image in Figure 7b cannot be used when hyperpolarised contrast agents are used but instead the flip angle needs to be reduced to 5. The image then obtained is shown in Figure 7c, wherein the SNR is again 19.4. Hence, the LS method produces an equivalent SNR to the GE method in the case of hyperpolarised contrast agents but the scan time is significantly reduced.

EXAMPLE 2 - Point Scanning Method

Figure 8 of the accompanying drawings shows the results from simulations using both PS and CSI sequences.

In Figure 8a, an image generated by the PS method is shown and has a SNR of 17.6. The image in Figure 8b is from a CSI sequence with a long TR, the latter to ensure full relaxation between excitation pulses, and a flip angle of 90. In this case, the SNR is 2230. However, the sequence leading to the image in Figure 8b cannot be used when hyperpolarised media are used but instead the flip angle needs to be reduced to 0.45. The image then obtained is shown in Figure 8c, wherein the SNR is again 17.6. Hence, the PS method produces an equivalent SNR to the CSI method in the case of hyperpolarised media.

EXAMPLE 3 - FISP Sequence Method

Figure 9 of the accompanying drawings shows the results of simulations of experiments with hyperpolarised imaging agents. Figure 9a shows an image using hyperpolarised ^3He gas using an FISP sequence wherein TR/TE/FA = 20/3/4. The T_1 value was 36 secs, whilst T_2 was 3 ms. This is an example wherein T_2 is short and it is clear that a good SNR is obtained due to the small flip angle. Figure 9b also shows an image using hyperpolarised ^3He gas but in this case the FISP sequence has TR/TE/FA = 20/3/90. Once again, the T_1 value was 36 secs and the T_2 value was 3 ms. In this case, the large flip angle causes the SNR to be low.

In Figure 9c, ^{13}C is imaged using an FISP sequence wherein TR/TE/FA = 80/75/5. In this case, T_1 is 30 secs and T_2 is 30 secs in the outer region, whilst T_1 is 30 secs and T_2 is 2 secs in the inner region. This is an example wherein both T_1 and T_2 are long. With the small flip angle employed, the contrast between the two regions is poor. In Figure 9d, ^{13}C is again imaged but in this case the FISP sequence has TR/TE/FA = 80/75/90. T_1 and T_2 values are as for Figure 9c. In this case, the large flip angle ensures that the SNR is high and the T_2 contrast is significantly improved.

Claims

1. A method of magnetic resonance imaging of a sample, said method comprising:
i) administering a hyperpolarised MR imaging agent comprising non-zero nuclear spin nuclei into said sample;
ii) exposing said sample to a radiation at a frequency selected to excite nuclear spin transitions in said non-zero nuclear spin nuclei;
iii) detecting MR signals from said sample and utilising spectral-spatial excitation, in combination with line scanning, point scanning and/or steady state imaging techniques; and
iv) optionally generating an image, physiological data or metabolic data from said detected signals.

2. The method as claimed in claim 1 wherein step iii) is carried out after the agent has left the vascular bed.

3. The method as claimed in claim 1 or 2 wherein for steady state imaging a fully balanced version of gradient sequences is used.

4. The method as claimed in any of the claims 1 to 3 wherein for steady state imaging FISP or PSIF pulse sequences with high flip angles are used.

5. The method as claimed in any of the claims 1 to 4 wherein said non-zero nuclear spin nuclei are selected from the group consisting of ^{1}H, ^{3}He, ^{3}Li, ^{13}C, ^{15}N, ^{19}F, ^{29}Si, ^{31}P and ^{129}Xe.

6. The method as claimed in any of the claims 1 to 5 wherein said non-zero nuclear spin nuclei are selected from the group consisting of ^{13}C and ^{15}N, especially ^{13}C nuclei.

7. The method as claimed in any one of the claims 1 to 6 wherein said MR imaging agent is artificially enriched with nuclei having a T_1 relaxation time of more than 5s.

8. The method as claimed in claim 6 wherein the MR imaging agent has an effective nuclei ^{13}C polarisation of more than 1%.

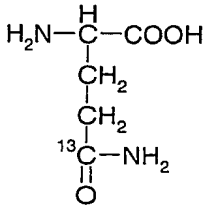
9. The method as claimed in claim 6 wherein the MR imaging agent is ^{13}C enriched at carbonyl or quaternary carbon positions.

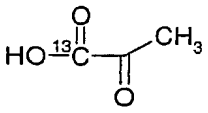
10. The method as claimed in claim 9 wherein said ^{13}C enriched compound is deuterium labelled adjacent said ^{13}C nucleus.

11. The method as claimed in any one of claims 6 to 10 wherein said ^{13}C nuclei are surrounded by one or more non-MR active nuclei or entities selected from the group consisting of O, S, C or a double or triple bond.

12. The method as claimed in any of the claims 1 to 11 wherein step iii) utilises spectral-spatial excitation combined with a steady state imaging technique.

13. The method as claimed in any of the claims 1 12 wherein said imaging agent comprises a compound selected from the following:





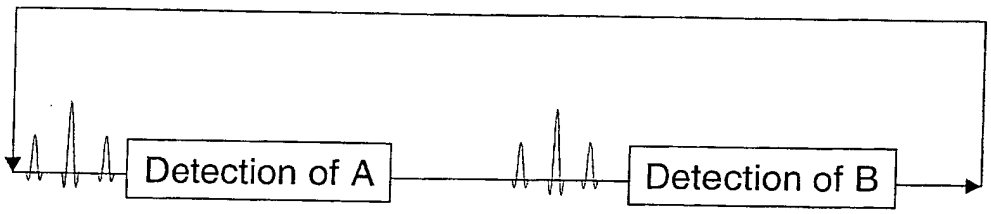


Fig. 1

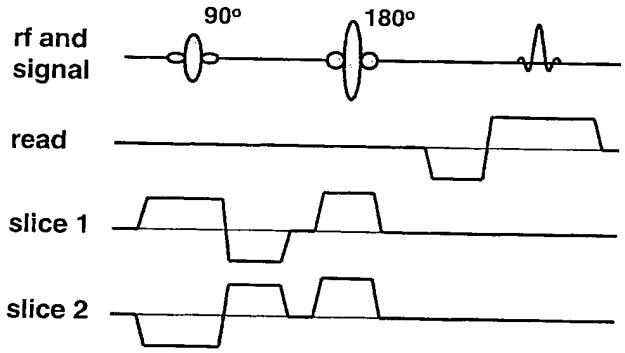


Fig. 2

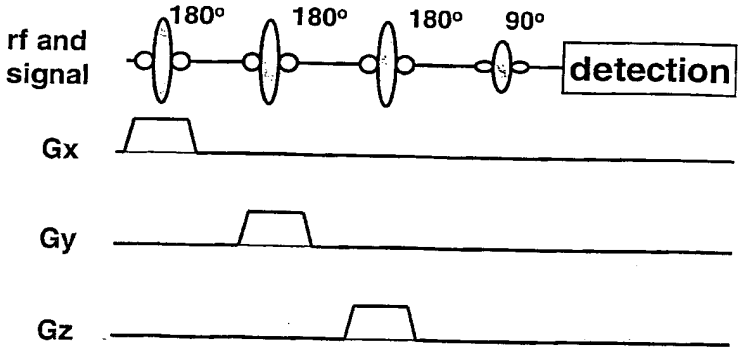


Fig. 3

Fig. 4

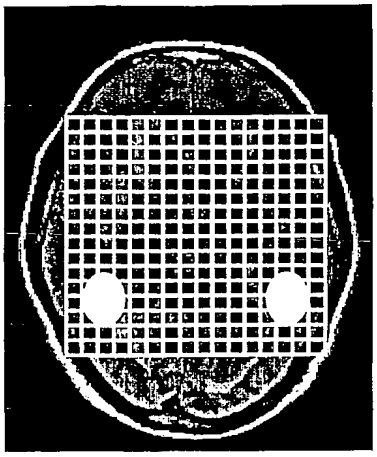
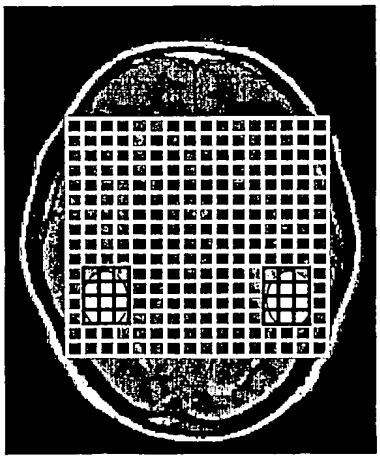


Fig. 5



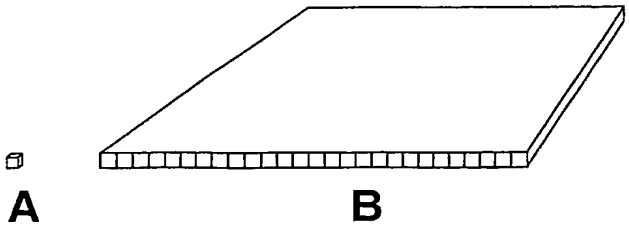


Fig. 6

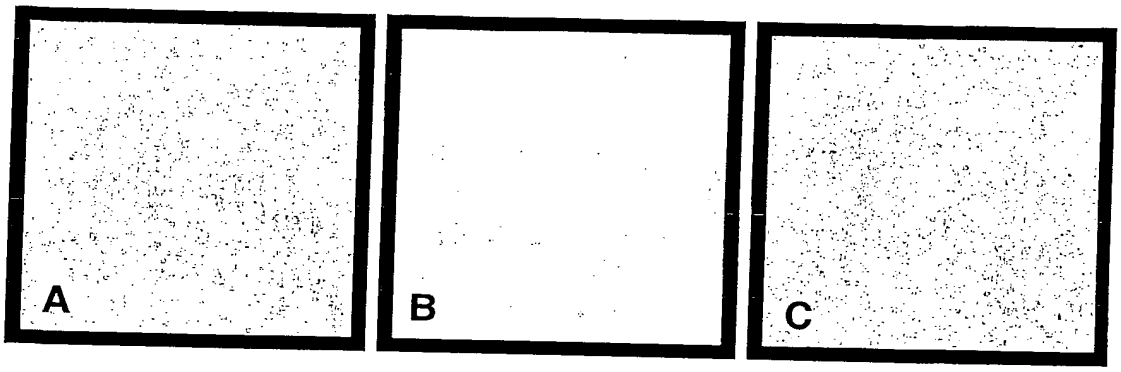


Fig. 7

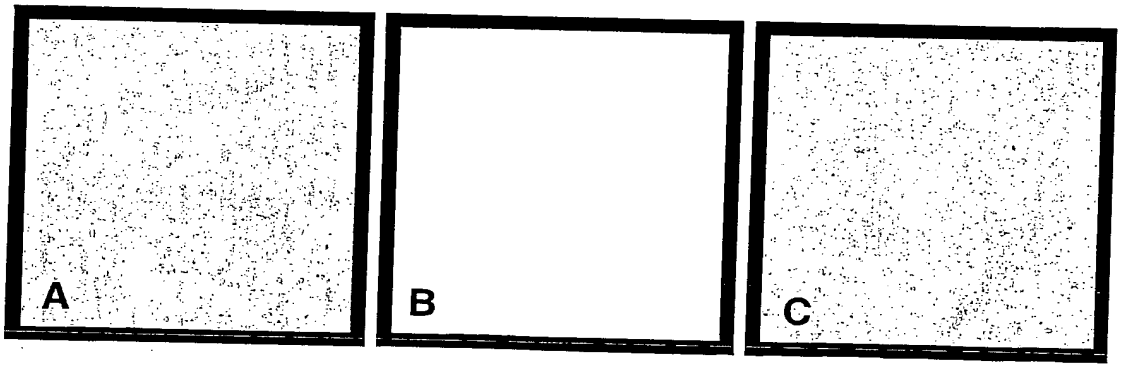
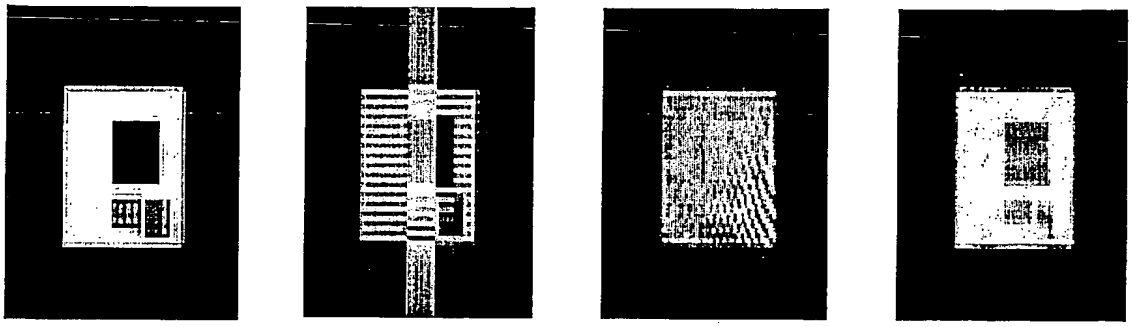


Fig. 8



a b c d

Fig. 9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NO 02/00321

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01R33/28 A61K49/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01R A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2002	08. 01. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	STURE ELNÄS/JA A

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